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DOI:

[10.1002/wps.20367](https://doi.org/10.1002/wps.20367)

Document Version

Peer reviewed version

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Citation for published version (APA):

Young, A., & Colasanti, A. (2016). Carving depression at its joints? *World Psychiatry*, 15(3), 239-241.
<https://doi.org/10.1002/wps.20367>

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Carving depression at its joints?

Personalization of treatments has long been an aspiration for medicine and has recently evolved into a sophisticated practice for the treatment of some diseases. Although in psychiatry treatment decisions are usually based on the individual patient and his/her needs, there is a lack of information about how the benefits and harms of individual pharmacological agents (and indeed treatments in other modalities) differ from patient to patient and very limited data on which to base the choice between treatment options for individual patients. The thoughtful paper by R. Perlis¹ addresses the challenges in personalization of antidepressant treatment and highlights various important scientific questions thereof.

Perlis suggests that available phenomenological patient-level features may be of more help than generally acknowledged for establishing probability of response. Whilst many might have sympathy with this view, history is replete with debates about the therapeutic utility of various subdivisions of depression, perhaps most notably the prolonged dispute between the Newcastle categorical² and the Maudsley dimensional³ approach. Such arguments remain inconclusive.

However, other recent work has focused on the cases of depression which have undiagnosed bipolar disorder and highlighted this as an area potentially important for personalizing treatment. The seminal paper by Angst et al⁴ showed that broad diagnostic criteria (in comparison with DSM-IV-TR criteria) identified a large number of additional patients with major depressive episodes who were likely manifesting depression as part of a bipolar disorder. These authors suggest that additionally considering family history, illness course and clinical status, as well as diagnostic criteria, may provide useful information for physicians when assessing evidence of bipolarity in patients with major depressive episodes. Many such patients (with major depressive episodes as part of a bipolar disorder) will be treated with but not respond to antidepressants. This has led to the notion being promulgated that all antidepressants should be, as a regulatory requirement, tested in bipolar major depressive episodes as well as in unipolar depression⁵.

Perlis also reviews biological approaches, but the question remains: are the currently available putative biomarkers of antidepressant response really more robust and consistent tools compared to “artisanal” practice? For example, the correlation between plasma drug levels and clinical response is weak and not only are drug plasma levels poorly associated with doses of drugs, but there is also a significant dissociation between brain and plasma kinetics, as demonstrated by positron emission tomography (PET) receptor occupancy studies⁶. Many factors, other than plasma levels, moderate drug action in the central nervous system. These factors will affect the predictive ability of pharmacogenomic biomarkers that are directly linked to pharmacokinetic variables, for example those which are genetic determinants of drug metabolism, and limit their potential contribution in increasing precision of pharmacotherapies.

The development of high precision pharmacotherapies is typically driven by the combination of three factors: a) treatments are potentially highly efficacious if the right treatment is given to the right person; b) treatments are very expensive; c) treatments may be associated with serious adverse effects. The need for careful pre-selection of a specific treatment for the right patients becomes highest in those diseases in which it is most important to direct expensive investments to the patients identified with highest-benefit and lowest-risk potential. For mood disorders as a whole, there is arguably less of a compelling need for this kind of “precision” treatments: pharmacotherapies for depression are relatively affordable, compared to those for autoimmune or neoplastic diseases, and very serious adverse effects are rare. Thus, clinicians may end up trusting more their own

“artisanal” judgment based on experience than not very informative evidence-based medicine inspired treatment protocols and guidelines.

The integration of multimodal biomarker approaches may potentially increase precision but at the moment their cost and complexity is high and the utility of this approach unproven. New biomarker approaches (transcriptomic, proteomic, genomic and telomeric) may potentially change this⁷. However, it will be important to establish how much higher remission rates can be achieved with such multimodal biomarkers informing personalized treatment before advocating this approach. Even if this could not be translated into clinical practice because of cost and complexity, proof of concept would answer crucial clinical research questions that have remained unresolved despite the overall progress in neuroscience.

Where does all of this leave us? It may be worthwhile pausing to reflect on how progress was achieved recently in other fields of medicine. Although we often feel that our problems are unique to psychiatry, the confounding effects of heterogeneity are not confined to mood disorders and have been addressed in other fields of study by focussing on the most reliable diagnoses which are most tractable for research⁸. This has produced major advances in the understanding of genetics in Alzheimer’s disease, which have underpinned ongoing therapeutic research. This approach has also been shown to be practical in familial studies of lithium response⁹. Extending this approach further to mood disorders might mean focussing, for instance, on bipolar I disorder with a strong familial component. We could apply this “narrow” approach to therapeutic research in this area and combine it with the multimodal biomarker notions outlined above. Any relationship between biomarkers and therapeutic responses could then be further verified in larger clinical populations.

What of “broad” approaches, i.e. studying a multiplicity of factors in large groups of heterogeneous patients? This will undoubtedly continue and may be made potentially more fruitful by recent developments. The recent revision of DSM introduced new ways of splicing major depression, including the delineation of various facets of the clinical symptomatology. An interesting example of the potential advantages of this development is a recent study on major depression with mixed features¹⁰.

Future progress will likely come from the application of both “narrow” and “broad” approaches, focussed on valid and well characterized patient samples, trying, to quote Socrates, to “divide things again by classes, where the natural joints are”.

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